Remarks

Formal Matters

Claims 1, 3-8, 20, 22-25 remain in this application. Claims 1, 20 and 22 are amended. Claims 2, 9-19, 21 and 25-50 have been canceled. No new matter is added by the amendments.

Support for the amendments is found generally throughout the specification, and specifically at least as indicated below:

Claims 1, 20: Page 3, line 11.

Claim 22: Page 4, lines 3-4.

In view of the Examiner's earlier restriction requirement, applicant retains the right to present withdrawn and/or cancelled subject matter in continued prosecution.

The Rejection Under 35 U.S.C. § 102(e)

Claims 1, 3-8 and 20 are rejected under 35 U.S.C. § 102(e) as being anticipated by US2003/0138417, as evidenced by US2004/0191243.

Specifically, the Examiner asserts that the '417 publication discloses stable, isotonic liquid, pharmaceutical antibody formulations comprising 50 mM histidine buffer, 0.03% polysorbate at pH 6 (Ex. 8, para. 104). The Examiner further asserts that the '417 publication discloses that this pharmaceutical formulation can be used in stabilizing IgE antibody formulations at concentrations greater than 100 mg/ml (abstract, claims 2-3) with about 200 mM tonicity modifier such as arginine (para. 52). Additionally, the Examiner asserts that '417 teaches an isotonic formulation with an osmotic pressure from 270-328 mOsm (para. 29), as well as stable antibody formulations that prevent aggregation and increased storage time for various methods of administration. (paras. 2, 13-15). In response, neither the '417, the '243 or any combination of the disclosures of these two references teach the claimed formulation of rhuMAbE25 antibody.

The '417 reference discloses IgE as a target for Abs in a long laundry list. Thus, '417 does not appreciate that each antibody acts distinctly in solution, which is especially the case

with rhuMAbE25. This fact is corroborated in the Liu *et al.* reference which describes that each Ab is different, and that one can't assume that each Ab in para. 23 of '417 can be used interchangeably with the same excipients with the expectation of similar rheological properties. The Examiner has apparently dismissed Liu *et al.* for failing to disclose whether or not the claimed range is enabled, as well as the density value so that the viscosity values can be compared to those of the '417 reference.

In response, Applicants respectfully submit that the density in the Liu et al reference is recited on page 1930 (last paragraph, left column) as 1.05 g/L. Moreover, the antibody identified in Liu as MAb1 is in fact, rhuMAbE25, the subject of the presently claimed subject matter.

Applicants further amend the claimed subject matter to specify that the antibody is rhuMAb E25, in order clarify the claim and strengthen Applicants' argument that the prior art does not suggest the particular claimed combination of excipients and ranges. Responsive to the Examiner's comments about the Lui *et al.* reference submitted with the last response, the point was to show that viscosity can vary greatly dependent upon the specificity of the antibody, which further strengthens Applicants' selection argument.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 3-8 and 20 are rejected under 35 U.S.C. § 102(e) as being anticipated by US2003/0138417, as evidenced by US2004/0191243.

The First Rejection Under 35 U.S.C. § 103(a)

Claims 1, 16, 17, 22-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US 2003/0138417 as evidenced by US 2004/0191243 in view of U.S. Pat. No. 5,994,511.

Specifically the Examiner asserts that the '417 is a proper anticipatory reference and the combined teachings of the references renders the claims obvious. Applicants' arguments were directed to the '243 reference, not the '417 reference.

While the '243 reference does specifically describe arginine as an excipient, this reference does not specifically describe any antibody in a stable liquid formulation of 120 - 260 mg/ml. In fact, most of the specific examples recite antibody concentrations of 50 mg/ml, with the highest concentration specifically described is 100 mg/ml of ABX-IL8, in Examples 12 and

15. While Example 16 of '243 does describe 150 mg/ml after purification, this was only in the context of a viscosity measurement, not for an evaluation of a stable formulation. Moreover, the histidine concentration in this solution was only 5 mM, which is outside the claimed range. The '243 reference does not describe liquid anti-IgE formulations.

These deficiencies are not remedied through combination with the '511 patent. While the '511 patent teach anti-IgE antibodies, it does not each liquid formulations of such antibodies at a concentration of 120 - 260 mg/ml. As a result, none of the references, in any combination teach, a stable, liquid formulation of (1) rhuMAbE25 anti-IgE antibodies in a concentration of 120 - 260 mg/ml, (2) arginine-HCl in an amount of 50 to 200 mM, (3) histidine in an amount of 10 to 100 mM, (4) polysorbate in amount of 0.01 to 0.1%, further having a pH of 5.5 to 7.0, a kinematic viscosity of about 50 cs or less, an osmolarity ranging from 200 mOsm/kg to 450 mOsm/kg and the claimed turbidity measurement.

As confirmed by Liu *et al.*, rhuMAbE25 behaves differently in solution from other antibodies, and thus the selection of the particular combination of excipients is a selection is non-obvious and patentable. With respect to Liu *et al.*, The Examiner's attention is directed specifically to Figure 1, which is a graph of concentration v. viscosity. At a concentration of about 120 mg/ml, the viscosity is already 50 mPas. Divided by the density of 1.05, this roughly converts to 47.6 kinematic viscosity. Thus, without the particular combination of excipients in the claimed range, any formulation of the claimed antibody would have a viscosity in excess of 50 cs and would be outside of the claimed subject matter.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 16, 17, 22-25 under 35 U.S.C. § 103(a) as being unpatentable over US 2003/0138417 as evidenced by US 2004/0191243 in view of U.S. Pat. No. 5,994,511

The Second Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-8, 16, 17, 20 and 22-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/26909, in view of U.S.P. 5,994,511.

Specifically, the Examiner asserts that the '909 publication teaches a stable protein formulation comprising 10 mM histidine, 160 mM arginine-HCl, a pH of 7, a protein concentration of about 160 mg/ml and 0.05 % polysorbate. The Examiner further asserts that

such a formulation would inherently possess the additional claimed properties of low turbidity, 50 cs or less kinematic viscosity and osmotic pressure from 270 - 328 mOsm.

In response, Applicants respectfully submit that the Examiner is ignoring Applicants point that the anti-IgE antibodies of the invention, when formulated at high concentrations, do not behave in manner similar to that of other antibodies. This fact is supported by the previously supplied Liu et al. reference discussed above. The Examiner's attention is directed specifically to Figure 1, which is a graph of concentration v. viscosity. At a concentration of about 120 mg/ml, the viscosity is already 50 mPas. Divided by the density of 1.05, this roughly converts to 47.6 kinematic viscosity. Thus, without the particular combination of excipients in the claimed range, any formulation of the claimed antibody would have a viscosity in excess of 50 cs and would be outside of the claimed subject matter.

As a result, none of the references, in any combination teach, a stable, liquid formulation of (1) anti-IgE antibody rhuMAbE25 in a concentration of 120 - 260 mg/ml, (2) arginine-HCl in an amount of 50 to 200 mM, (3) histidine in an amount of 10 to 100 mM, (4) polysorbate in amount of 0.01 to 0.1%, further having a pH of 5.5 to 7.0, a kinematic viscosity of about 50 cs or less, an osmolarity ranging from 200 mOsm/kg to 450 mOsm/kg and the claimed turbidity measurement.

Applicants respectfully request reconsideration and withdrawal of Claims 1, 3-8, 16, 17, 20 and 22-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/26909, in view of U.S.P. 5,994,511.

Judicially Created Double Patenting Rejection

Claims 1, 3-8, 16, 17, 20 and 22-25 are rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-4, 7-13, 22-27, 31-34, 37-42, 48, 51-56, 58 and 59 of U.S. Patent No. 6,875,432 in view of U.S. 2004/109243.

Specifically, the Examiner asserts that the '432 patent teaches a stable antibody formulation comprising about 80-130 mg/ml of rhuMAbE25, histidine buffer, arginine-HCl and polysorbate in Claims 1-4, 7-13, 22-27 and 31-34. The Examiner acknowledged that there is no disclosure for the particular concentration ranges of histidine, arginine and polysorbate.

The Examiner further asserts that the '243 publication teaches a particular range of histidine of 10-50 mM, arginine-HCl of about 60 mM and polysorbate at 0.01 to 0.1%.

In response, Applicants have amended the claimed range of arginine to specify a minimum about of 100 mM, which is outside of the explicitly enumerated amount in the '243 reference. As a result, the '243 reference does not suggest a range of the enumerated excipients that overlaps with the claimed range.

Applicants respectfully request reconsideration and withdrawal of the double patenting rejection over Claims 1-4, 7-13, 22-27, 31-34, 37-42, 48, 51-56, 58 and 59 of U.S. Patent No. 6,875,432 in view of U.S. 2004/109243.

The Rejections under 35 U.S.C. § 112, First and Second Paragraph

Claims 1, 3-8, 16 and 17 have been rejected both for allegedly (1) being indefinite as well as (2) failing the written description requirement. Specifically, the Examiner has rejected to the usage of the language "or equivalent."

In response, Applicants' amendment renders the rejection moot.
Applicants respectfully request reconsideration and withdrawal of both rejections of Claims 1, 3-8, 16 and 17 under 35 U.S.C. § 112, First and Second paragraph.

SUMMARY

Claims 1, 3-8, 20, 22-25 are pending in the application

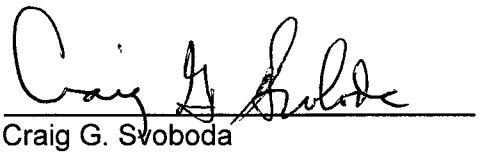
If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is strongly encouraged to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and petition for a 3-month extension of time and fees. If fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
GENENTECH, INC.

Date: March 5, 2008

By: 

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